2014-1391

United States Court of Appeals for the Federal Circuit

PAR PHARMACEUTICAL, INC. and
ALKERMES PHARMA IRELAND LIMITED,

Plaintiffs – Appellants,

v.

TWI PHARMACEUTICALS, INC.,

Defendant – Appellee.

Appeal from the United States District Court for the District of Maryland in case no. 11-CV-02466-CCB, Judge Catherine C. Blake

BRIEF OF THE DEFENDANT-APPELLEE TWI PHARMACEUTICALS, INC.

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JULY 31, 2014

CERTIFICATE OF INTEREST

Pursuant to FED. CIR. R. 47.4, counsel for Appellee TWi Pharmaceuticals, Inc. certifies the following:

1. The full name of every party represented by me is:

TWi Pharmaceuticals, Inc.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

The party named in the caption is the real party in interest.

3. All parent corporations and any publicly held companies that own 10% or more of the stock of the party represented by me are:

TWi Pharmaceuticals, Inc. is a publicly held stock company of Taiwan with no parent corporation. Although no longer a wholly owned subsidiary, TWi Pharmaceuticals Holdings, Inc. has a financial interest in TWi Pharmaceuticals, Inc. No publicly held corporation owns more than ten (10) percent of TWi Pharmaceuticals, Inc. or TWi Pharmaceuticals Holdings, Inc.

4. The names of all law firms and the partners or associates that appeared for the party now represented by me in the trial court or agency or are expected to appear in this court are:

Don J. Mizerk, Steven E. Feldman, Daniel R. Cherry, and John A. Sholar, all of Husch Blackwell LLP Chicago, Illinois.

/s/ Don J. Mizerk
an Attorney for Defendant-Appellee
TWi Pharmaceuticals, Inc.

July 31, 2014
Date

TABLE OF CONTENTS

TABLE OF AUTHORITIES

CASES

STATUTES

OTHER AUTHORITIES

STATEMENT OF RELATED CASES

No appeal in or from this same civil action in the lower court was previously before this or any other appellate court.

No other cases are known to counsel to be pending in this Court that will directly affect or be directly affected by this Court's decision in the pending appeal.

The following case is pending in district court and could potentially be affected by this appeal: *Par Pharm., Inc. and Alkermes Pharma Ireland Ltd. v. Breckenridge Pharm., Inc.*, No. 1:13-cv-01114 (D. Del.).

STATEMENT OF THE ISSUE

Did the District Court err by holding the asserted claims of the patent-in-suit invalid for obviousness?

INTRODUCTION

Prior art patents, owned by one Appellant and licensed to the other, expressly identified megestrol acetate as a drug to be nano-sized and taught how to do it. The inventors of the patent-in-suit merely followed those prior art teachings, then made measurements of the resulting blood serum concentrations. That is not patentable. *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) ("[A]n obvious formulation cannot become unobvious simply by administering it to a patient and claiming the resulting serum concentrations.").

COUNTER-STATEMENT OF THE CASE

I. The proceedings in the District Court.

A. The patent-in-suit.

Appellants Par Pharmaceutical, Inc. ("Par") and Alkermes Pharma Ireland, Limited ("Alkermes") sued TWi Pharmaceuticals, Inc. ("TWi") for infringement of U.S. Patent No. 7,101,756. (A2.) The patent's effective filing date is April 12, 2002. (A10.) The patent issued to Alkermes (then known as Elan). (A16; A43.) Par is licensed under the patent-in-suit and Alkermes' prior art patents. (A6344; A6375-A6376; A3054 at 13:4-14:7; A3074-A3075 at 96:6-97:16.) The patent-in-suit covers the use of Par's Megace ES medication, a nanoparticulate formulation

of megestrol acetate used to treat anorexia, cachexia, and unexplained weight loss in patients with HIV and AIDS. (A2.) The parties stipulated that, under the Court's claim constructions, use of TWi's ANDA products would infringe the patent-in-suit. (A27624-A27625.)

The patent-in-suit's Abstract states that "[t]he present invention is directed to nanoparticulate compositions comprising megestrol." (A43.) Alkermes' now expired prior art Liversidge patents had already disclosed and claimed nano-sizing megestrol acetate. (A22; A25-26; A3052 at 7:13-19; A3104-A3106 at 82:10-90:21; A14879 at 3:25-26; A14937; A14947-A14948 (Claim 1).)

The patent-in-suit's "Background of the Invention" concludes with the statements that "[t]here is a need in the art for megestrol formulations which exhibit [1] increased bioavailability, [2] less variability, and/or [3] less viscosity as compared to conventional microparticulate megestrol formulations" and that "[t]he present invention satisfies those needs." (A55 at 4:28-32 (bracketed numerals added).) Prior art references, including the Liversidge patents, had already taught that nanoparticulate technology [1] increased bioavailability, [2] lessened variability, and [3] lessened viscosity. (A22-A24; A35; A3100-A3104 at 67:3-84:4; A3115-A3116 at 21:6-27:24; A14890 at 3:3-5; A14905; A14917; A14925; A14955-A14956; A14958; A14994; A15709.)

Both independent claims of the patent-in-suit are method claims with two parts. They first recite what to do:

> A method of increasing the body mass in a human patient suffering from anorexia, cachexia, or loss of body mass, comprising administering to the human patient a megestrol formulation, wherein:
>
> (a) the megestrol acetate formulation is a dose of about 40 mg to about 800 mg in about a 5 mL dose of an oral suspension;
> (b) the megestrol acetate formulation comprises megestrol particles having an effective average particle size of less than about 2000 nm, and at least one surface stabilizer associated with the surface of the megestrol particles; and
> (c) the administration is once daily;….

(A74-A75.) As a shorthand, we will refer to these recitations as the "what-to-do" recitations.

Both independent claims conclude with three wherein clauses that recite what one gets when the what-to-do recitations are followed. Claim 1 recites:

> wherein after a single administration in a human subject of the formulation there is no substantial difference in the C_{max} of megestrol when the formulation is administered to the subject in a fed versus a fasted state,
> wherein fasted state is defined as the subject having no food within at least the previous 10 hours, and wherein fed state is defined as the subject having a high-calorie meal within approximately 30 minutes of dosing.

(A74-A75.) C_{MAX} is the maximum plasma concentration of the drug. (A74 (Tables 12, 13).) Claim 4 differs from Claim 1 by reciting that "the difference in the C_{MAX} of the megestrol when administered in a fed versus a fasted state is

selected from the group consisting of less than about 100% [other members of the Markush group omitted]." (A75.)[1] Claim 5 depends from Claim 4 and specifies a difference of less than about 60%. (A75.) As a shorthand we will refer to these recitations as the "food effect" recitations.

Dependent Claims 2, 10, 21, and 24 recite treating HIV or AIDS. (A75-A76.) Dependent Claims 16-17 and 30-31 recite the use of certain types of surface stabilizers. (A75-A77.) The remaining asserted dependent claims have additional recitations concerning the C_{MAX} obtained when the what-to-do recitations are followed. (A75-A77.)

B. The District Court held all the asserted claims invalid for obviousness.

After a bench trial, the District Court held all the asserted claims of the patent-in-suit invalid for obviousness. (A2.)

The District Court found that the prior art disclosed all the elements of the asserted claims. (A25.) See Section III of this Counter-Statement Of The Case. For example, the Court found that the prior art included Megace OS, a micro-sized formulation of megestrol acetate that was used to treat the same condition claimed in the patent-in-suit. (A10.) The Court further found that prior art Liversidge

[1] The other members of the Markush group need not be considered in determining obviousness. *Fresenius USA, Inc. v. Baxter Int'l, Inc.*, 582 F.3d 1288, 1298 (Fed. Cir. 2009).

patents identified megestrol acetate as a drug to be nano-sized and taught how to do it. (A21-A22; A25-A26.)

The Court determined that "[g]iven that all the elements are disclosed in the prior art, the essential inquiry for determining obviousness in this case is whether a person of ordinary skill in the art would have seen a benefit to applying the nanoparticulate technology disclosed in the prior art to Megace OS and have been motivated to do so." (A28.) The Court found that "it was known that Megace OS was viscous and required more dosing and that absorption levels varied greatly among patients." (A29.) It further found "that both of these problems provided sufficient motivation for a person skilled in the art to create a method of treatment using nanoparticles." (*Id.*) The Court found that these problems "were known to be affected by a drug's particle size." (A32; *accord*, A33 ("The benefits of reducing particle size were known with respect to all known problems").) Accordingly, the Court found that "a person skilled in the art thus would have been motivated to use the [nanoparticulate] technology to improve upon all known problems with one solution." (A31.)

The District Court found a reasonable likelihood of success. (A35-A36.) Specifically, the Court found that a person skilled in the art would have believed:

- That "making nanoparticles was not extremely difficult." (A35; *see also id.* (The prior art described "its 'simplicity.'").)

- That it "could successfully be implemented with a wide variety of drugs, particularly steroids." (A35; *see also id.* (The prior art provided "several examples of success.").)
- That it "would result in reduced interpatient variability, improved bioavailability, reduced viscosity and reduced dosing volumes." (A35; *see also id.* ("[T]he expected benefits of nanoparticles were widely touted by 2002.").)

In rejecting Appellants' attacks on a reasonable expectation of success, the Court found that "[t]here is no evidence to suggest a person of skill in the art, in 2002, would have believed anything other than that nanotechnology was sufficiently simple to apply and would result in the claimed benefits as TWi has shown with extensive evidence." (A36.)

The District Court found that the claimed reduction in food effect was an inherent property. (A26-A28.) The Court, therefore, held that this property could not save the otherwise obvious method from invalidity. (*Id.*) It relied on this Court's precedents, including *Santarus* and *In re Kao*, 639 F.3d 1057 (Fed. Cir. 2011).

The District Court found that the evidence did not support Appellants' "teach away" arguments, such as the one based on Appellants' "distort[ion]" of the Graham reference. (A33.)

"Before making its final conclusions with respect to obviousness," the District Court considered the proffered evidence of objective indicia of nonobviousness. (A36.)

First, the District Court rejected Appellants' assertion that "reduced food effect" and "increased weight gain" were unexpected results. (A37 n.20 ("[T]he improvements do not appear to be more than might be predicted given the known improvements in efficacy associated with nanotechnology.").) In addition, the Court found that, even if these results were unexpected, that would not undermine the Court's finding that ample motivations to nano-size Megace OS were provided by nanotechnology's known ability to address interpatient variability and volume/viscosity problems. (A37.)

Second, the District Court found that Appellants' proffered evidence of long-felt need was not commensurate with the scope of most of the asserted claims. (A38.) As to the remaining claims, the Court found that the evidence was not sufficient to show the meeting of a previously unmet need. (A39.)

Third, the District Court rejected Appellants' reliance on alleged "copying." (A39, citing authorities explaining that copying is not probative of obviousness in ANDA cases.) On appeal, Appellants assert no error in this finding. (Appellants' Bf. 57.)

Fourth, with regard to alleged commercial success, the District Court found:

- That Megace ES had only a 19% share of the megestrol acetate market. (A41.)
- That some of the alleged commercial success may have been due to features that were not novel. (A40.)
- That Par boosted its sales by engaging in criminal conduct. (A41.)

The Court stated, "After discounting sales and market share figures for Par's criminal conduct, and considering that some portion of sales may be due to the touting of non-novel features, the court does not find evidence of commercial success that persuasively undermines the claimed invention's obviousness." (A41.) On appeal, Appellants assert no error in these findings. (Par Bf. 57.)

After considering all the evidence, the District Court concluded that TWi had shown by clear and convincing evidence that the asserted claims are invalid for obviousness. (A42.)

The District Court did not decide TWi's nonenablement, unpatentable subject matter, and lack of standing defenses. (A2 n.1.)

II. Appellants' Megace ES program was not innovative, was deceptively promoted, and did not meet expectations.

A. Appellants' inventors did not invent nano-sizing technology, and they were not the first to disclose nano-sizing megestrol acetate.

The ability of an orally ingested drug to enter the bloodstream is referred to as its bioavailability. (A3112 at 11:14-12:5.) Improving a drug's solubility

increases its bioavailability. (A14; A3100 at 68:1-20; A3112 at 11:3-12:5; A14889 at 1:12-16.) Reducing the drug's particle size increases its solubility by increasing its surface area. (A24; A31; A3100 at 68:1-20; A14889 at 1:28-31; A14975; A14990-A14992.) Surface stabilizers maintain the increased surface area by retarding the tendency of the reduced-sized particles to agglomerate. (A3088 at 18:7-12; A3113 at 15:10-16:25.)

Megestrol acetate is a steroid used to treat loss of appetite. (A3; A3091 at 30:17-20; A3104 at 81:21-22.) Bristol Meyers Squibb had already improved upon earlier megestrol acetate formulations by using micronizing technology to reduce the average particle size to about 3 to 10 microns and, starting in 1993, sold the resulting product as "Megace OS." (A2-A3; A6020 at 2:53-54.)[2]

Nanoparticulate technology was "the next developmental step" for even further reducing particle size. (A15704.) A nanometer is 1,000 times smaller than a micron. (A3088 at 20:17-25.) In about 1990, Liversidge *et al.* pioneered and patented the "Nanocrystal" technique involving "wet milling in the presence of grinding media in conjunction with a surface modifier." (A3026 at 103:6-8; A14888; A14890 at 3:5, 18-20; A14976-A14977; A15704.) Prior to the Liversidge method, particles could be readily reduced to a few hundred nanometers, but could not maintain that small size because they would

[2] Using micronization to improve drug bioavailability is discussed in *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1343-44 (Fed. Cir. 2009).

agglomerate into larger clumps. (A3024-A3025 at 96:7-99:8; A14904.) The Liversidge method overcame that problem and produced pharmaceutical compositions having average particle sizes less than 400 nm and displaying "unexpectedly high bioavailability" with "improved dose proportionality" and "decreased fed-fasted variability." (A23; A35; A14890 at 3:5; A14905; A14916-A14917; A14925; *see also* A3101 at 72:2-4 (Liversidge's technique "was certainly a breakthrough.").)

Articles published in 2000 described how nano-sizing techniques had been developed that provided long-term stability, that large scale machines were available for performing the nano-sizing, and that the "major advantages of this technology are its general applicability to most drugs and its simplicity." (A15703; *see also* A14988 ("years of storage"); A14994-A14995 ("Large-volume pearl mills are available thus allowing the large-scale production of these formulations."); A15709 ("long-term stability"); A3053 at 9:14 ("We never failed.").)

Liversidge identified megestrol acetate as a drug to be nano-sized in a U.S. patent issued in 1995 and claimed nano-sizing a megestrol acetate cancer agent in an European patent application published in 2000. (A22; A25-A26; A3104-A3106 at 83:23-84:13, 85:1-7, 86:10-24, 88:1-89:25; A14877 at [45], [57]; A14879 at 3:25-26; A14937 at (45); A14947-A14948 (claim 1).) These patents have since expired in 2011. (A3052 at 7:13-19.)

In late 2001, Par asked Elan (now known as Alkermes) to nano-size Par's generic version of Megace OS. (A3; A16; A27-A28 n.18; A31; A17014 at 92:9-93:01.) By then, Elan was in the business of making nano-particulate formulations for client companies on a fee-for-service basis. (A17002-A17003 at 17:7-18:5.) Elan considered Par's request to be a "routine project." (A3066 at 62:12-17.) The task was assigned to Dr. Pruitt, who had just been hired upon completion of his graduate work, as his first project. (A16979-A16982 at 9:25-17:21.) He had not previously worked with a nanoparticulate formulation. (A16980 at 13:1-10.) He quickly succeeded in nano-sizing the megestrol acetate using the prior art Liversidge method owned by Elan. (A3; A3021-A3022 at 84:5-86:1; A14996; A15616; A15704; A15811-A15815; A16987-A16989 at 38:1-55:12; A17020 at 124:22-125:17.)

Appellants acknowledge that the inventors did not know about Megace OS's food effect problem. (Appellants' Bf. 52-53.) It was not even their idea to test for a food effect; that was suggested by others in the industry. (A3189 at 106:11-107:2; A15874; A15581; A16993 at 98:6-11; A17015 at 97:12-98:3.) When they filed for a patent, their only data was for healthy patients, and so they depended on prior art experience with micro-sized Megace OS when they claimed nano-sized megestrol acetate would be medically useful. (A3092 at 35:22-36:9; A3120 at 41:17-42:1; A3188 at 102:4-6 ("Q. There is no pharmacodynamic testing at all in

the ’576 patent, correct? A. That’s correct.”), 103:1-7 (“Q. Now the only reason that the inventors state that nanoparticulate formulations could be suitable for any indication is because the existing non-nanoparticulate formulations were used for the indication, correct? (Pause) A. Yes. I believe that’s a correct statement.”).)

B. Par pled guilty to falsely claiming that Megace ES has superior clinical efficacy over Megace OS.

In 2013, Par pled guilty to misbranding Megace ES from 2005 to 2009 by, among other things, claiming superior clinical efficacy over Megace OS without conducting relevant clinical studies. (A5 n.4; A41; A16242-A16245.) At the plea and sentencing hearing, Par’s CEO testified:

> Q During the period from July 2005 through 2009, did Par promote Megace ES as a more effective product than its competitor Megace OS?
>
> A Yes.
>
> Q Do you admit that Par lacked adequate or sufficient data from well-controlled clinical trials to support its claims of Megace ES’s superior clinical efficacy over Megace OS?
>
> A Yes.
>
> Q Do you admit that Par’s claims between July 2005 and 2009 that Megace ES had superior clinical efficacy over Megace OS were false and/or misleading because Par lacked adequate or sufficient data from well-controlled clinical trials to support those claims?
>
> A Yes.

(A16240-A16241.) The Par-sponsored study reported in the 2007 Wanke paper, on which Appellants extensively rely (Appellants' Bf. 3, 8-9, 24, 49, 63-64), was the only study comparing the efficacy of Megace ES and Megace OS that Par had. (A3221 at 62:15-63:8; A6077; A6274.) As Dr. Beach testified, "[T]here were significant problems with that study…." (A3118 at 35:9-11.)

C. Megace ES did not meet sales projections and has attained only a modest market share.

Megace ES has never met any of its revenue or prescription targets. (A3284 at 65:21-23.) Megace ES's share of the megestrol acetate market peaked at 23% and has since fallen to 19%. (A41.) This shows "that physicians haven't embraced this product as offering clinical benefits over what's currently available." (A3289 at 87:23-25.) The District Court found that what little commercial acceptance Megace ES achieved was due in part to Par's criminal conduct. (A41.)

III. The claim limitations do not distinguish from the prior art.

A. The patent does not claim a new use, dose, mode or frequency of administration.

The District Court found that everything recited in the preamble and transitional phrases of the independent claims about using megestrol acetate to treat weight loss reads on the prior art Megace OS product. (A10; A25; *see* A3152 at 43:20-44:17; A6056; A14932; A15940; A16605 at (57).) The Court also found that the "40 mg to about 800 mg" and "oral suspension" limitations in clause (a) read on Megace OS. (A10; A25; *see* A6056; A14892 at 7:53-60; A14928;

A14930-A14931; A14936; A15940; A16605 at (57).) In addition, the Court found that the "once daily" limitation of clause (c) was taught by the prior art once daily administration of Megace OS. (A10; A25; *see* A6045; A6056; A6069; A14936.)

B. The particle size and volume limitations simply recite the result of nano-sizing.

Megace OS has particles too large to meet the "less than about 2000 nm" limitation in clause (b) of the claims. However, the District Court found that prior art references expressly identified megestrol acetate as a compound to be nano-sized. (A22; A14947-A14948 at Claim 1; A14878-A14879 at 3:22-26, 2:18-20.) For example, Claim 1 of the prior art Liversidge EPO '215 reference recites, "A process for obtaining a composition comprising nanoparticles consisting essentially of: (a) a crystalline anticancer agent selected from the group consisting of … megestrol acetate…." (A14947-A14948.) It further specifies use of "a surface modifier" and "an average particle size of less than 400 nm." (A14948; *see also id.* ("less than 300 nm") (claim 3.).)

The District Court also found that additional prior art references disclosed nano-sized particle sizes within the "less than about 2000 nm" limitation of clause (b) (A20; A22; *see* A14884 at claims 1-3; A14888 at [57]; A14905; A14921-A14924 at Table 1; A14943 at [0052]; A14963; A14964; A14977; A15653 at claims 1-5; A15633; A15705; A15730 at claims 1-5), as well as the use of a "surface stabilizer" as recited in clause (b). (A20; A22; *see* A14884 at 14:11;

A14888 at [57]; A14905; A14921-A14924 at Table 1; A14938 at [0006]; A14963; A14966; A14989; A15710; A15720 at [57]; A15634.)

The recited 5 mL amount in clause(a) is a teaspoonful. (A3189 at 107:12-17 ("The inventors…did not invent the teaspoon, using a teaspoon as a dosage for medicine.").) Although it is less than Megace OS's recommended 20 mL dose, a substantial reduction in dose volume would have been expected from nano-sizing's further reduction of particle size. (A23; A14936; A14958; A14993; A15633-A15634; A15723 at 5:67-6:4; A15646 at 6:5-9; A3061 at 44:17-25; A14961.)

C. The claims measure food effect by comparing Fed C_{MAX} and Fasted C_{MAX}.

The three concluding "wherein" clauses of independent Claims 1 and 4 recite the degree of food effect present when the what-to-do recitations are followed. See Section I.A of this Counter-Statement Of The Case. They measure food effect by comparing the C_{MAX} obtained after a single administration in the fed state with the C_{MAX} obtained after a single administration in the fasted state. Par calls the former Fed C_{MAX} and the latter Fasted C_{MAX}. (Appellants' Bf. 6 n.1.)

Claims 4 and 5 assign percentages to the difference between Fed C_{MAX} and Fasted C_{MAX}. (A75.) Instead of assigning a number, Claim 1 states that there is "no substantial difference" between Fed C_{MAX} and Fasted C_{MAX}. The District Court construed this limitation as "not limited only to formulations with an *absence* of food effect" but as also including formulations in which "the effect was

not 'substantial'" such that "the drug could be taken 'without regard to meals,' and yet still be clinically effective in the claimed dose." (A21542 (Court's italics).)

The specification states several times that "C_{MAX} (ng/ml) = Maximum plasma concentration." (A67 (Tables 2 and 3); A74 (Tables 12 and 13).) At one point the specification states, "As used herein, the phrase 'maximum plasma concentration' is interpreted as the maximum plasma concentration that megestrol will reach in fasting subjects." (A66 at 25:6-9.) However, the concluding "wherein" clauses of Claims 1 and 4 refer to C_{MAX} measurements in both the fed state as well as the fasted state. In addition, on several occasions the written description refers to C_{MAX} in fed subjects. (A57 at 8:39-40; A67 (Table 3); A68 at 29:35-30:1; A74 (Table 13).) The District Court did not construe C_{MAX} to refer only to fasted subjects, and neither party asked it to do so. (A25133-A25158; A20071-A20089.)

None of the claims recite anything about the existence of a food effect in prior art Megace OS. Dependent Claims 7 and 19 are the only claims that refer to prior formulations. (A75-A76.) Those two claims add the requirement that going from a micron-sized to a nano-sized formulation must produce an increase in C_{MAX} of about 5% or more. (*Id.*) They recite nothing about the difference between Fed C_{MAX} and Fasted C_{MAX} in prior art formulations.

D. No food effect problem would have been expected from nano-sized megestrol acetate.

The claimed lack of an appreciable difference between Fed C_{MAX} and Fasted C_{MAX} would have been expected from nano-sizing Megestrol OS.

Megestrol acetate is a BCS Class II drug, which means that it has "solubilit[y] too low to be consistent with complete absorption" even though it is "highly membrane permeable." (A14; A16465; A3106 at 92:13-15; A3107 at 95:11-96:5 (The BCS System places drugs into one of four categories according to their solubility and permeability.).) BCS Class II drugs are typically more bioavailable when administered with a high fat meal. (A3108 at 97:1-19.) The fat content causes secretion of additional bile acid and enzymes that increase the dissolution rate of the drug. (A3108 at 97:6-15.) Par's expert admitted that he knew of "no research or study whatsoever that megestrol acetate did not follow that general rule." (A3209 at 13:3-22; A16594-A16595.)

An improvement in bioavailability reduces this food effect. (A3112 at 11:11-13.) With higher bioavailability the drug dissolves in the gastro-intestinal fluids without needing the assistance of the food. (A3112 at 11:25-12:5.)

Reducing particle size was a known strategy for improving bioavailability, and micro-sizing was a way to do that. (A24; A31.) Because micro-sized Megace OS had not yet been tested for a food effect at the time of the invention, the

District Court found that the POSA would not have known whether a food effect problem existed after micro-sizing the drug. (A13; A19.)

Nano-sizing was a known strategy for even further reducing particle size. (A23, citing A14905, A14925, A14955-A14956; A14994; A15634; A15721 at 1:36-51; *see also* A14917; A15709.) Accordingly, the District Court rejected Appellants' request for a finding that the absence of an appreciable food effect in nano-sized megestrol acetate was unexpected. (A37 n.20 ("do[es] not appear to be more than what might be predicted given the known improvements in efficacy associated with nanotechnology").

E. The lack of an appreciable food effect is an inherent property of having nano-sized Megace OS.

The limitations about the lack of an appreciable difference between Fed C_{MAX} and Fasted C_{MAX} do not add any additional steps to, or change the formulations recited in, the what-to-do portions of the claims. They only recite measurements of properties obtained after following the what-to-do recitations. The Court held that these were inherent properties that did not support validity over the prior art. (A26-A28.) As Dr. Beach explained, the reduction in particle size improves bioavailability, so that the assistance of the additional bile and enzymes stimulated by digestion of fatty foods is no longer needed. (A27; A3107-A3108 at 96:14-97:19; A3112 at 10:24-12:5; *see also* A17011 at 79:14-80:6; A17013 at 90:20-91:9.)

F. The dependent claims do not distinguish from the prior art.

The record also supports the District Court's findings that the remaining asserted claims also do not differentiate from the prior art. (A25-A28.)

1. The "HIV or AIDS" dependent claims.

Dependent Claims 2, 10, 21, and 24 recite that the anorexia, cachexia or loss of body mass being treated is associated with "HIV or AIDS." (A75-A76.) Prior art Megace OS was used for that purpose. (A10; A25.)

2. The dependent claims reciting a 5% improvement in mean C_{MAX} compared to nonnanoparticulate megestrol.

Dependent Claims 7 and 19 recite that the claimed formulation "exhibits a mean C_{MAX} selected from the group consisting of greater than about 5%, [other members of Markush group omitted], than the mean C_{MAX} exhibited by a standard commercial, nonnanoparticulate composition of megestrol, administered at the same dosage." (A75-A76.)

The modest 5% increase was not surprising given that "[t]he prior art disclosed… increased C_{MAX} levels in formulations with reduced particle sizes." (A25 citing A15938.) For example, the prior art "disclosed that nanoparticulate formulations of two steroids, Steroid A and danazol, demonstrated seven and sixteen fold increases, respectively, in bioavailability over conventional formulations when tested in dogs." (A22; *see also* A37 n.20; A14895 at 13:64-

14:4; A14916-A14917; A14924-A14925; A14955-A14956; A14969; A14994; A15709.).

3. The dependent claims reciting a minimum C_{MAX}.

Dependent Claims 13 and 27 recite that "the maximum blood plasma concentration of megestrol is at least about 700 ng/ml and is attained in less than 5 hours after administration of the megestrol formulation." (A75-A76.) Dependent Claims 14 and 28 are the same, except they recite "400 ng/ml" instead of 700 ng/ml. (*Id*.) Dependent Claims 12 and 26 recite "700 ng/ml," but do not have the "less than 5 hours" requirement. (*Id*.) The specification defines "about" to mean "plus or minus 10%" (A56 at 6:34-35), and so the recitation of "at least about 700 ng/ml" goes as low as 630 ng/mL. Claims 12-15 and 26-28 do not specify that it is the concentration reached after a single administration in the fasted state.

The prior art Graham study reports a mean C_{MAX} of 828 ng/mL with a mean T_{MAX} of 3.6 hours. (A15930 (Table 2).) The specification of the patent-in-suit acknowledges similar numbers for prior art Megace OS. (A59 at 11:26-29 ("According to the package insert of Megace®, the pharmacokinetic profile of the oral suspension contains parameters such that the median T_{MAX} is 5 hours and the mean C_{MAX} is 753 ng/ml."); A3091-A3092 at 32:23-33:1; A14929.)

4. The dependent claims reciting a range for mean C_{MAX} after a single administration in a fasted state.

Dependent Claims 15 and 29 recite that "a mean C_{MAX} of about 300 ng/ml to about 2000 ng/ml is obtained after a single administration of the formulation in the human subject in a fasted state." (A75-A76.) The patent defines "about" as meaning "plus or minus 10%" (A56 at 6:32-35), and so the claimed lower and upper limits are 300 $\pm$ 30 ng/mL and 2000 $\pm$ 200 ng/mL.

While Appellants' witnesses did not explain the origins of these limits, the numbers are similar to prior art numbers. The 300 $\pm$ 30 ng/mL lower limit matches the 300 ng/mL "threshold" found in the prior art Graham study to be sufficient to produce a "statistically significant correlation" to weight gain. (A6055.) The 2000 $\pm$ 200 nm/mL claimed upper limit overlaps with the 1400 $\pm$ 400 ng/mL reported in the patent-in-suit for prior art Megace OS. (A74 (Table 13, Ref. Treatment B); A72-A73 (Ref. Treatment B is Megace OS).) It is also near the highest level of C_{MAX}, 1,670 ng/mL, in the Graham study. (A6057 (Table 2).) While these prior art C_{MAX} measurements were in the steady state rather than after a single administration in the fasted state as recited in Claims 15 and 29, the patent-in-suit does not include any data establishing the claimed range under the claimed conditions. For example, the highest C_{MAX} reported in the patent's Table 12 (fasted data) is 950 $\pm$ 270 ng/mL, which does not correlate to the claimed maximum of 2000 $\pm$ 200 ng/mL. (A74.)

Achievement of a C_{MAX} sufficient to fall within the broad range recited in Claims 15 and 29 would have been expected after nano-sizing megestrol acetate because the prior art reported that measurements of C_{MAX} after a single administration in the fasted state improved after reductions in particle size. Farinha reported a nearly threefold improvement after micro-sizing megestrol acetate. (A15938.) Liversidge reported a fifteen fold improvement, as measured in dogs, when danazol was nano-sized. (A14969 (Table 1) (3.01 $\pm$ 0.80 μg/mL vs. 0.20 $\pm$ 0.06 μg/mL).) A seven fold improvement was reported for nano-sizing Steroid A. (A14895 at 13:55-14:4; A14925.)

5. The dependent claims reciting the use of particular surface stabilizers.

Dependent Claims 16-17 and 30-31 recite various surface stabilizers. (A75-A76.) The prior art discloses use of such stabilizers in both micro-sized megestrol suspensions and nano-sized ones. (A3096-A3097 at 52:14-53:7; A16610-A16611 (claims 4-9); (A14948-A14949 (claims 4 and 17); A3105 at 86:10-87:7; A14939 at [0020]-[0021]; A14879 at 3:61-4:52; A14890-A14891 at 4:34-5:12.)

SUMMARY OF ARGUMENT

The District Court found that:

- The prior art taught how to nano-size a drug. (A20-A24; A35-A36.)
- The prior art expressly identified megestrol acetate as a drug to be nano-sized. (A22.)

- The known interpatient variability and volume/viscosity problems with Megace OS would have motivated the person of ordinary skill in the art ("POSA") to nano-size it. (A23-A33.)
- The POSA would have had a reasonable expectation of success. (A35-A36.)
- The prior art did not teach away. (A33-A35.)
- The lack of a food effect problem was not unexpected. (A37 n.20.)
- The lack of appreciable food effect was an inherent property. (A26-A28.)
- Appellants failed to prove objective indicia of nonobviousness. (A36-A41.)

Obviousness is the only conclusion that can be drawn from the District Court's factual findings.

Appellants have failed to demonstrate clear error in any of those findings. Appellants' arguments are really just attempts to retry the case, which is exactly what Fed. R. Civ. P. 52(a)(6)'s clearly erroneous standard forbids. *Amstar Corp. v. Envirotech Corp.*, 823 F.2d 1538, 1543 (Fed. Cir. 1987) (Appellant "improperly asks this court to evaluate the evidence and find the facts *de novo*."); *Polaroid Corp. v. Eastman Kodak Co.*, 789 F.2d 1556, 1558, 1559 (Fed. Cir. 1986) ("[W]e

do not retry the case…. [N]or do we repeat the role of the trial judge in finding our own facts.").

As explained below in Argument Section I, there was no clear error in the District Court's findings that the prior art taught how to nano-size a drug, that the prior art specifically identified megestrol acetate as a drug to be nano-sized, that the POSA would have been motivated to nano-size Megace OS, that she would have expected success in doing so, and that the prior art did not teach away from doing it. No hindsight was needed or used by the District Court because the prior art provided ample teachings.

As explained below in Argument Section II, the District Court committed no clear error in rejecting Appellants' assertion that the differences between Fed C_{MAX} and Fasted C_{MAX} recited in the claims were unexpected. The claims say nothing about the difference between Fed C_{MAX} and Fasted C_{MAX} in the prior art micro-sized formulation; they only claim the absence of an appreciable food effect in the nano-sized formulation. No one would have been surprised by the absence of a food effect problem in the nano-sized formulation because it was known that food effects are ameliorated by nano-sizing. (A22-A24.)

As explained below in Argument Section III, there was no clear error in the District Court's finding that the lack of an appreciable food effect was an inherent property. The food effect recitations in the claims are merely measurements of Fed

C_{MAX} and Fasted C_{MAX}. Under *Santarus*, "an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations." 694 F.3d at 1354.

As explained below in Argument Section IV, there was no clear error in the District Court's findings regarding the alleged objective indicia of nonobviousness. Appellants failed to produce persuasive evidence of any unexpected result or fulfillment of an unmet need by the patented invention. They concede the District Court properly rejected their evidence of copying and commercial success.

When all the evidence is weighed on the "scales of patentability," the strong evidence of obviousness far outweighs the alleged evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966); *In re Lyons*, 364 F.2d 1005, 1016 (CCPA 1966).

STANDARDS OF REVIEW

"Obviousness is a question of law, reviewed *de novo*, based on underlying factual questions which are reviewed for clear error following a bench trial." *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006); *accord*, *In re Cyclobenzaprine*, 676 F.3d 1063, 1069 (Fed. Cir. 2012).

"Findings of fact, whether based on oral or other evidence, must not be set aside unless clearly erroneous, and the reviewing court must give due regard to the trial court's opportunity to judge the witnesses' credibility." Fed. R. Civ. P. 52

(a)(6). "Under the clear error standard, a reversal is permitted only when this court is left with a definite and firm conviction that the district court was in error." *Alza*, 464 F.3d at 1289. "The burden of overcoming the district court's factual findings is, as it should be, a heavy one." *Polaroid*, 789 F.2d at 1559. "[T]he 'clearly erroneous' standard does not entitle this court to reverse the district court's finding simply because it would have decided the case differently." *Miles Labs., Inc. v. Shandon Inc.*, 997 F.2d 870, 874 (Fed. Cir. 1993). "This is so even where the district court's findings do not rest on credibility determinations, but are based instead on physical or documentary evidence or inferences from other acts." *Anderson v. City of Bessemer City*, 470 U.S. 564, 574 (1985).

ARGUMENT

I. There was no clear error in the District Court's findings that the prior art pointed to the claimed invention.

The District Court did not need or use hindsight. The prior art pointed to the claimed invention.

A. There was no clear error in the District Court's findings that the prior art taught how to nano-size a drug and identified megestrol acetate as a drug to be nano-sized.

The "mother" Liversidge '684 patent taught the "breakthrough" wet milling technique for nano-sizing drugs. (A20-A21; A3023 at 91:20-92:7; A3101 at 70:22-71:14; A14889 at 2:31-34.) It disclosed that the technique was suitable for a "wide variety of drug substances," including steroids. (A20-A21; A14890 at 3:38-

39; A14892-A14895 (Examples 1-14); A14896 (Claim 5).) Its "[p]referred drug substances" included "those intended for oral administration." (A21; A14890 at 4:5-6.)

The Liversidge '363 c-i-p patent identified megestrol acetate as one of the drugs suitable for nano-sizing. (A22; A25-A26; A14877; A14879 at 3:25-26.) The Liversidge '215 European patent application claimed nano-sized megestrol acetate as an option in what in U.S. practice is called a Markush group. (A14947-A14948 (Claim 1).)

Appellants point to passages in the Liversidge patents describing lab testing for stability of "at least 15 minutes, and preferably, at least two days or longer after preparation." (Appellants' Bf. 16, 17 citing A14892 at 7:43-46, A14881 at 7:40-42.) Those are the parameters for "a simple screening process" for selecting an appropriate surface modifier, not a statement of the expected stability of the suspension. (A14892 at 7:21-46.) Because the patents disclose and claim pharmaceutical compositions, they teach to expect the stability needed to achieve that purpose. (A14889 at 1:8-9; A14892 at 8:10-12; A14896 (Claims 14-15); A14940-A14941 at [0035]-[0038]; A14947-A14948 (Claim 1).) By 2000, the literature reported nano-sized formulations with long-term stability. (A14988 ("years of storage"); A15709 ("long-term stability").) Achieving long-term stability was a matter of optimizing the surface stabilizer. (A14989 ("Storage of

drug nanoparticles as an aqueous suspension is principally possible if the stabilizing surfactant mixture is optimal.").)

For litigation purposes, Appellants now say that their own prior art nano-sizing technology was too iffy. (Appellants' Bf. 7, 15-18, 24, 26, 50). That was not the message that Appellant Alkermes publicized in its prior art patents, promotional materials, and scientific publications. (A14881 at 8:1-2 ("The selected dosage can be readily determined by one skilled in the art…."); A14953 ("Applicable to all dosage forms, including solid and liquid products for oral and parenteral application."); *id.* ("Consists of safe, pharmaceutically acceptable formulations."); A14964 ("This approach should have general applicability to many poorly soluble drugs with dissolution rate-limited absorption."); A15633 (Increased dissolution rate through particle size reduction "can be accomplished predictably and efficiently using NanoCrystal® technology."); *id.* ("An Enabling Technology"); A15582 ("it will certainly be more [bio]available"); A14909 ("effective amounts and treatment methods… can be readily determined by one of skill in the art.").)

Appellants say their prior art nano-sizing technology addressed only the "first step" of "creating the nanoparticles themselves" and not the remaining steps needed "to develop a marketed pharmaceutical product." (Appellants' Bf. 16-17, 50-51.) Appellants, however, never specify what those remaining steps were,

much less how they presented technical hurdles beyond the teachings of the prior art or the ordinary skill in the art. None are recited in the claims. *In re Huang*, 100 F.3d 135, 138 (Fed. Cir. 1996) ("[O]ur obviousness analysis focuses on the invention *as claimed*.") (court's italics). The prior art references regarded the remaining steps as being within the capabilities of the skilled worker. (A14881 at 7:52-8:5; A14889 at 2:35-37; A14892 at 7:53-8:20; A14896 (Claims 14, 15); A14925; A14941 at [0038]-[0039]; A3061 at 44:7-25; A14961.) Appellants' evidence came nowhere close to overcoming the presumption that the prior art Liversidge references are enabled. *In re Antor Media Corp.*, 689 F.3d 1282, 1287-88 (Fed. Cir. 2012); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003). Appellants' expert admitted that these patents were enabled. (A3208 at 10:24-11:4.)

Appellants cannot confine the teachings of the '363 patent and EPO '215 to injectable anticancer agents. (Appellants' Bf. 17.) Those patents include teachings of liquid oral administration. (A14881 at 7:58-59; A14941 at 34.) Appellants' own conduct belies limiting the patent's teaching to anticancer agents. Par took a license under the '363 patent in order to sell Megace ES and, in an earlier trial against Abraxis, Alkermes (then Elan) used Megace ES as an embodiment of what the '363 patent covered. (A3024 at 93:18-94:13; A3054 at 13:4-14:7.) Moreover, the District Court correctly observed that "[w]hatever the primary purpose of the

prior art, a person skilled in the art may find a teaching in addition to that purpose." (A25 n.17, citing *KSR Int'l Co. v. Teleflex Co.*, 550 U.S. 398, 421 (2007).) As discussed next, the District Court did not clearly err in finding that the prior art provided multiple motivations to take advantage of nano-sizing's benefits when megestrol acetate is used, as Megace OS was, to treat weight loss.

B. There was no clear error in the District Court's finding that the POSA would have been motivated.

Whether the POSA would have had motivation to make the claimed invention is a question of fact. *Alza*, 464 F.3d at 1289.

The Court found that the POSA would have had two motivations to nano-size Megace OS. (A28-A33.) One motivation was the patient compliance problem arising from having to take a half-cup dose of a viscous liquid. (A28-A29.) The other motivation was the high interpatient variability problem. (A29-A32.)

The District Court relied on the statement in the patent-in-suit's written description that "[t]ypical commercial formulations of megestrol, such as Megace, are relatively large volume, highly viscous substances that are not well accepted by patient populations, particularly subjects suffering from wasting." (A29 quoting A56 at 6:49-51.) The same point is made in the patent's Background Of The Invention. (A55 at 3:43-46.) These are binding admissions about the prior art. *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1361-62 (Fed. Cir.

2007); *Constant v. Adv. Micro-Devices, Inc.*, 848 F.2d 1560, 1570 (Fed. Cir. 1988).[3] The Court also cited (A10) Dr. Liversidge's description of the problem:

> The ingredient in [Megace OS] is megestrol acetate, that used to be sold as a big slimy formulation, it was very viscous. You had to take 30 milliliters, so 30 milliliters is I would say about a half cup maybe.

(A3063 at 52:4-8; *id.* at 52:8 ("[I]t's horribly slimy.").) Appellants criticize the District Court for not citing prior art publications discussing this volume/viscosity problem. (Appellants' Bf. 45-46.) However, it was not clearly erroneous for the District Court to credit the POSA with knowledge of what the patients and attending medical personnel knew from their own experiences with prior art Megace OS.

Appellants are wrong when they argue that the prior art did not teach that nano-sizing would address this volume/viscosity problem. (Appellants' Bf. 46.) As benefits of nano-sizing, Elan's 2001 promotional literature specifically touted reduced viscosity and smaller dose volume through improved dose proportionality. (A14955; A14958; A3113-A3116 at 14:13-15:3, 23:7-10, 25:23-26:10; A15634; *see also* A15646 at 6:6-9, 55-59; A15723 at 6:2-4, 48-52.) The Court cited (A10-

[3] The District Court found that a different statement in the specification saying there was a need for increased bioavailability was not an admission about the prior art, but rather "the inventors' own evaluation of the prior art." (A18.) By contrast, no evaluation by the inventors is involved in the specification's statement that patients did not like taking large volume/highly viscous Megace OS.

A11) Dr. Fleckenstein's testimony that one would have expected nano-sizing to help the problem:

> With the Megace OS, it was really a viscous type of material. It tended to coat the mouth and the throat.
>
> So, you know, a lot of these AIDS patients have difficulty swallowing, so it made more difficult to swallow, and it had kind of a gritty type of taste to it. So it was the viscosity and the consistency of it, really, that was a problem, yes.
>
> THE COURT: Wouldn't switching to the nanoparticulate formulation help with that problem?
>
> THE WITNESS: Well, it would be expected to. I mean that would be expected to, you know, reduce the viscosity and would be expected to perhaps help with the grittiness.

(A3183 at 83:8-21.) Dr. Beach testified that amelioration of the volume/viscosity problem is a necessary result of nano-sizing's reduction of particle size. (A3116 at 27:9-28:15.)

As for the interpatient variability problem, Appellants do not deny that the prior art knew of that problem. (Appellants' Bf. 47.) As the District Court found, several studies reported the interpatient variability problem. (A12-A13; A30; A6055; A6059; A6069; A15938; A15945.) Appellants argue, instead, that the POSA would not have used nano-sizing, or any other formulation adjustment, to address the interpatient variability problem. (Appellants' Bf. 47-49.)

The District Court was on solid ground in finding a motivation to use nano-sizing because the prior art taught that nano-sizing reduced interpatient variability.

(A23; A14994; A15643 at [57]; A15709; A15720 at [57].) The District Court found that, because the prior art taught that the absorption of BCS Class II drugs is dissolution-rate limited and that reducing particle size increases dissolution velocity, the POSA would have discerned from the prior art a suggestion that the interpatient variability problem arose from bioavailability problems that could be addressed with nanotechnology. (A31; A3112 at 10:24-11:24.) Although the cause of Megace OS's interpatient variability had not been established (A13), the District Court found that "[n]anotechnology would have been especially appealing" because two prior art references "attributed interpatient variability to a patient's wasting or changes in their gastrointestinal physiology" and the prior art taught that "nanoparticles' adhesion process was little affected by the nutritional status of the patient." (A31; A6059; A6069; A14994.)

Appellants argue that interpatient variability still persists even after nano-sizing, relying on the variation in weight gains reported in the Par-sponsored study reported in the 2007 Wanke paper, but citing no testimony to support this attorney argument. (Appellants' Bf. 49.) That study post-dates the invention and, therefore, could not have affected the POSA's motivations and expectations. Furthermore, that study was defective and is not conclusive for any of the propositions that Appellants cite it for. See Section II.B of the Counter-Statement Of The Case. For example, the 2007 Wanke paper states that it is "not clear how

much the degree of change in weight in this trial was limited by lack of access to food for participants" since the trials were conducted with patients "living predominantly in the resource-constrained countries of South Africa and India." (A6085-A6086.) Accordingly, one cannot draw reliable conclusions from the study's weight gain variation.

Appellants point to how some prior art references did not use nanotechnology to formulate megestrol acetate. (Appellants' Bf. 15, 52.) Because "silence does not imply teaching away," the failure of some references to discuss nano-sizing does not amount to a teaching away from it. *Allergan, Inc. v. Apotex Inc.*, Nos. 2013-1245, -1246, -1247, -1249, slip op. 19 (Fed. Cir. June 10, 2014).

Appellants argue that there were other ways besides nano-sizing to address these problems. (Appellants' Bf. 46-47, 48, 50.) Even were that true, obviousness is not defeated by the existence of other options, even preferable options, because TWi needed only to prove that nano-sizing was a suitable choice, not the best one. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013); *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1376 (Fed. Cir. 2013); *Santarus*, 694 F.3d at 1355-56, *Syntex (USA) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005); *In re Gurley*, 27 F.2d 551, 553 (Fed. Cir. 1994); *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989).

Either one of the two motivations found by the District Court would suffice for obviousness. Taken together, they would have provided the POSA with particularly strong impetus to nano-size Megace OS because, as the Court found, by nano-sizing the drug the POSA would have expected to be able to improve on both problems with the same approach. (A31.)

Appellants complain that these motivations are not aimed at obtaining the patent-in-suit's claimed C_{MAX} measurements. (Appellants' Bf. 30-35.) Appellants concede, however, that a motivation is sufficient if it results in the claimed invention, even if it is not the patentee's motivation. (*Id.* 33.) *See KSR*, 550 U.S. at 419-20. Here, the District Court found two motivations to nano-size Megace OS and, as explained below in Argument Section III, the claimed C_{MAX} measurements are inherent results of nano-sizing.

Appellants' cited cases are inapposite. (Appellants' Bf. 32-34.) Three do not discuss inherency. *ActiveVideo Networks, Inc. v. Verizon Comms., Inc.*, 694 F.3d 1312 (Fed. Cir. 2012); *In re Cyclobenzaprine*; *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363 (Fed. Cir. 2008). In two others, the district courts found that, unlike here, inherency had not been proved. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1294 (Fed. Cir. 2013); *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1351 (Fed. Cir. 2008). In Appellants' remaining case, most of the claims were invalid because the patent itself established inherency. *Alcon Research, Ltd. v. Apotex*,

Inc., 687 F.3d 1362, 1369 (Fed. Cir. 2012), *cert. denied*, 133 S. Ct. 1736 (2013). Two claims survived an obviousness challenge, not because of lack of inherency, but because they were specifically limited to the commercial dose (0.1% w/v) and the prior art taught away from that dose. *Id.* at 1370-71. Here, by contrast, Appellants do not argue that the claimed "about 40 mg to about 80 mg" and "5 mL" dose parameters are critical. *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004) (obviousness not avoided by recitation of noncritical parameter); *In re Boling*, 292 F.2d 306, 312 (CCPA 1961) (same). As explained in Sections III.A and III.B of the Counter-Statement Of The Case, those parameters are not distinguishable from the prior art. *Merck v. Biocraft*, 874 F.2d at 809 ("Reached by means of routine procedures, and producing only predictable results, the recited dosages therefore do not distinguish the claims of the '430 patent from the [prior art].").

C. There was no clear error in the District Court's finding that the POSA would have expected success.

Whether the POSA would have had a reasonable expectation of success is a question of fact. *Alza*, 464 F.3d at 1289; *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165-66 (Fed. Cir. 2006). Obviousness requires only a reasonable expectation of success, not certainty. *Allergan v. Sandoz,* 726 F.3d at 1292; *PharmaStem*, 491 F.3d at 1362, 1363; *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007); *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

The District Court found that a person of ordinary skill in the art would have had a reasonable likelihood of success. (A35-A36.) Specifically, the Court found that a person skilled in the art would have believed that "making nanoparticles was not extremely difficult," that it "could successfully be implemented with a wide variety of drugs, particularly steroids," and that it "would result in reduced interpatient variability, improved bioavailability, reduced viscosity and reduced dosing volumes." (A35; *see* A14881 at 7:51-8:5; A14890 at 3:32-4:20; A14906; A14997.) In rejecting Appellants' attacks on a reasonable expectation of success, the District Court found that "[t]here is no evidence to suggest a person of skill in the art, in 2002, would have believed anything other than that nanotechnology was sufficiently simple to apply and would result in the claimed benefits as TWi has shown with extensive evidence." (A36.)

None of these findings were clearly erroneous. Appellants are wrong when they characterize nanoparticulate technology as an utterly unproven endeavor in 2002. (Appellants' Bf. 14-18.) As explained above in Argument Section I.A and Section II.A of the Counter-Statement Of The Case, the technology had progressed in the decade between the filing of the Liversidge patents and the filing of the patent-in-suit. In 2001, prior to the exigencies of litigation, Elan (*i.e.*, Alkermes) touted its prior art Nanocrystal technology as predictable and efficient. (A15633.)

Appellants point out that in 2002 only one nano-sized drug had been FDA-approved. (Appellants' Bf. 50) The District Court, however, was well within its authority to credit Dr. Beach's testimony that, with a new technology like nano-sizing, the ten year incubation period between the issuance of Liversidge's groundbreaking prior art '684 patent and the first commercial product was not out of line. (A20; A3146 at 17:11-18:23.) Furthermore, as Dr. Beach testified, the Liversidge patents discouraged use outside of Elan. (A3146 at 18:24-19:18.)

D. There was no clear error in the District Court's finding that the prior art did not teach away.

Whether a prior art reference teaches away is a question of fact. *Medichem*, 437 F.3d at 1165. The District Court rejected Appellants' "teach away" arguments, finding that they "distort[] the teaching of Graham." (A33.) On appeal, Appellants persist in misreading the Graham reference.

No direct teaching away from Appellants' claimed invention appears in the Graham reference. It makes no comment about how to modify drug formulations, much less about nano-sizing in general or about nano-sizing megestrol acetate in particular. (A34; A6055-A6061.) The only prior art references that mention both nano-sizing and megestrol acetate are ones that encourage nano-sizing it. (A22; A25-A26; A14878-A14879 at 1:48-52, 3:22-26; A14947-A14948 at Claim 1.) Thus, the prior art taken as a whole taught toward, not away from, nano-sizing megestrol acetate. *Medichem*, 437 F.3d at 1165-66 (All the prior art must be

considered.); *Para-Ordnance Mfg., Inc. v. SGS Importers Int'l, Inc.*, 73 F.3d 1085, 1090 (Fed. Cir. 1995) (same).

Having no evidence of a direct teach away, Appellants attempt to conjure an indirect one by mischaracterizing the Graham reference. Relying on what happened in the second of two groups of patients, Appellants argue that Graham taught that the rapid absorption of the drug is undesirable and that efficacy was not correlated to the total amount of drug. (Appellants' Bf. 11-12, 53-55.)

To begin with, Appellants do not argue that there was anything unusual about what happened with the first group of patients (the 1-compartment group). Appellants, therefore, cannot mount an attack on the POSA being motivated to help patients of that type.

As to the four patients in the second group (the 2-compartment group), Appellants say those patients gained no weight. (Appellants' Bf. 12.) In fact, Graham reports that two of these four patients did gain weight. (A6057, Table 2 (patients 1 and 4).) No general conclusions can be drawn when the sample is so small and the data is inconsistent. While the study reported a rapid decline in the drug's plasma concentration in patients displaying rapid absorption, the study was not designed to test whether rapid absorption caused the rapid decline in plasma concentration, and so no one could properly draw that conclusion from the sparse, inconsistent data. In addition, the District Court found that the prior art suggested

that nano-sizing would "contribute to higher concentration levels for longer time periods." (A34 citing A15634.) Appellants criticize this finding without citing any contrary prior art suggesting that nano-sizing would not have this effect. (Appellants' Bf. 55-56.)

The Graham reference, as well as other prior art studies, show that higher doses have improved efficacy. (A3098-A3099 at 57:25-64:10.) Graham discusses two prior studies in which higher doses produced greater weight gains. (A12; A6059 (800 mg vs. 100 mg and 400 mg); *id.* (460-640 mg vs. 320 mg); A3098 at 60:7-10 ("Q. What would that tell a person of ordinary skill in the art in 2002? A. Simply putting more drug, higher blood level, more opportunity for a therapeutic effect.").) As to their own work, the authors of the Graham reference report that "[f]urther evaluation" of their data "revealed a statistically significant relation between weight gain and the percentage of the 24-h dosing interval that plasma megestrol concentrations exceeded a 300-ng/ml threshold (Fig. 2)." (A6060; *see also* A3099 at 62:3-23.) The later prior art Von Roenn study, with a larger patient population, showed that there was a direct correlation between the amount of drug administered and both the amount of weight gained and the number of patients who gained weight. (A12; A3099 at 63:8-64:10; A15940; A15942 at fig. 1.)

Appellants also argue that the Graham reference's data would suggest that improvement would be obtained with an extended-release dosage. (Appellants'

Bf. 55-56.) The Graham reference does not say anything about extended-release. Rather, Appellants rely on their expert's testimony that an extended release dosage is the way to go, but he admitted that there were no references suggesting that approach in the 40 years that megestrol acetate had been in use. (A3209 at 14:21-15:2.) Even if it were true that extended release was an option, even the preferred option, that does not amount to a teaching away from all other options. *Galderma*, 737 F.3d at 738; *Bayer v. Watson*, 713 F.3d at 1376; *Santarus*, 694 F.3d at 1356; *Syntex*, 407 F.3d at 1380; *Gurley*, 27 F.3d at 553; *Merck v. Biocraft*, 874 F.2d at 807. Indeed, there is no evidence that the extended release and nano-sizing options are incompatible, and so the teaching of one does not exclude the other.

II. There was no clear error in the District Court's finding that the POSA would not have expected nano-sized megestrol acetate to have an appreciable food effect.

The nonobviousness requirement assures that "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." *KSR*, 550 U.S. at 427. As discussed above in Argument Section I.A and Section II.A of the Counter-Statement Of The Case, the Liversidge prior art patents identified and claimed megestrol acetate as a drug to be nano-sized and instructed how to do it. There was no innovation in Appellants' inventors doing that.

For alleged innovation Appellants assert a "double showing" of unexpected results: (1) the "discovery" of the food effect problem in the prior art Megace OS

formulation and (2) the "solution" to that previously unknown problem. (Appellants' Bf. 58.) However, the Fed C_{MAX} and Fasted C_{MAX} measurements recited in the claims are of the claimed nano-sized formulation, not the prior art micro-sized formulation. Accordingly, the asserted claims say nothing about the *existence* of a food effect in *prior art* micro-sized formulations. (A74-A77.) What the claims recite is the ***non****existence* of a substantial food effect in the *claimed* nano-sized formulations. Ignorance or knowledge of a prior art food effect problem is simply not claimed. Accordingly, the relevant issue is the expectedness of a lack of an appreciable food effect in the claimed nano-sized formulations, not the discovery of a food effect problem in the prior art.

Because the phraseology "reduced food effect" has been frequently used throughout the case, this brief also uses it from time to time, but the reader is asked to keep in mind that it is only a shorthand and that the claims do not compare the food effect of the claimed method to the prior art. An "obviousness analysis focuses on the invention *as claimed*." *Huang*, 100 F.3d at 138 (court's emphasis). The claims only require that any food effect that may be present as a result of following the steps of the claimed method must be within certain parameters, *i.e.*, "no substantial difference" between Fed C_{MAX} and Fasted C_{MAX} (Claim 1) or a difference within certain percentages (Claims 4 and 5), irrespective of what those parameters may have been in the prior art. (A74-A75.)

Whether an alleged invention has produced an unexpected result is a question of fact reviewed for clear error after a bench trial. *Bristol-Meyers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 978 (Fed. Cir. 2014); *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1355-56 (Fed. Cir. 2013); *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1583 (Fed. Cir. 1996). The District Court rejected Appellants' assertion that the "reduced food effect" was "unexpected." (A37.) The Court explained that the claimed invention's improvements "do not appear to be more than what might be predicted given the known improvements in efficacy associated with nanotechnology." (*Id.* n.20.) There was no clear error in this.

The POSA would have appreciated that reduction of particle size was a known way to reduce food effect problems, and that both micro-sizing and nano-sizing did that. See Section III.D of the Counter-Statement Of The Case. Because Megace OS had not yet been tested for food effect, the POSA would not have known whether micro-sizing had taken care of any food effect issue. (A13; A19.) She would have reasoned, however, that if in fact Megace OS had no appreciable food effect, then nano-sizing would be unlikely to introduce one since the prior art taught that nano-sizing reduced food effects.[4] She would have further reasoned

[4] Appellants point to Dr. Fleckenstein's testimony about nano-sizing sorafenib having created a food effect. (Appellants' Bf. 39 citing A3168 (21:25-23:1).) However, unlike megestrol acetate, sorafenib is not a steroid and is not listed in the

that if a food effect problem remained after Megace OS's micro-sizing, then further particle size reduction by nano-sizing would take care of it. Prior art successes with other steroids would have reinforced this expectation. (A3116 at 27:11-13 ("Danazol had a fed/fasted effect that was eliminated basically by implementation of NanoCrystal technology."); *id.* at 27:14-15 ("Steroid A also had a fed/fasted effect that was essentially eliminated by NanoCrystal technology."); A14956.)

Accordingly, the POSA would have expected there would be no food effect appreciably affecting the administration of nano-sized megestrol acetate, meeting the District Court's construction of "no substantial difference" in Claim 1, as well as the 100% and 60% differences specified in Claims 4 and 5. There is no evidence that the claimed percentages are critical. *Iron Grip*, 392 F.3d at 1322 (Recitation of a specific number must be "critical" to support patentability.); *Boling*, 292 F.2d at 312 (same).

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prior art Liversidge patents as a drug to be nano-sized. (A3078 at 9:21-10:11.) Furthermore, Dr. Fleckenstein was relying on an unpublished report of work done after 2003. (*Id.* at 10:12-22.) The POSA's expectations would not have been affected by something unknown to her. Accordingly, the District Court correctly rejected this evidence. (A36 n.19.) Likewise, Appellants cite an FDA document dated December, 2002, which is also too late to be prior art considered by the POSA. (Appellants' Bf. 14; A6024.)

III. There was no clear error in the District Court's finding that the reduced food effect was an inherent property.

As just explained, the food effect limitations add nothing patentable because they are what the POSA would have expected from applying prior art nanotechnology to the prior art Megace OS product. In addition, they do not aid patentability because they are merely inherent properties.

A. An obvious formulation cannot be made nonobvious by measuring and claiming the resulting blood serum concentrations.

In *Santarus* this Court held that "an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations." 694 F.3d at 1354. That is exactly the situation here. The food effect recitations in Claims 1, 4 and 5 are simply measurements of Fed C_{MAX} and Fasted C_{MAX}.

As the *Santarus* court explained, simply claiming the serum concentrations resulting from an otherwise obvious formulation does not avoid invalidity because "[t]o hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." 694 F.3d at 1354; *see also Kao*, 639 F.3d at 1070 (The applicant's "claimed 'food effect' adds nothing of patentable consequence" because "the claimed 'food effect' is an inherent property.").

Over thirty years ago, the CCPA rejected the type of argument Appellants make here:

> [Applicants] are, in effect, arguing that a structure suggested by the prior art, and, hence, potentially in the possession of the public, is patentable to them because it also possesses an Inherent, but hitherto unknown, function which they claim to have discovered. This is not the law. A patent on such a structure would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art.

In re Wiseman, 596 F.2d 1019, 1023 (CCPA 1979); *accord, Alcon*, 687 F.3d at 1369; *In re Kubin*, 561 F.3d 1351, 1357-58 (Fed. Cir. 2009).

To support Appellants' notion that patentability should attach to the discovery of the prior art food effect problem in Megace OS, Appellants rely on *Eibel Process Co. v. Minn. & Ont. Paper Co.*, 261 U.S. 45 (1923); *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346 (Fed. Cir. 2013); *In re Nomiya*, 509 F.2d 566 (CCPA 1975); and *In re Sponnoble*, 405 F.2d 578 (CCPA 1969). (Appellants' Bf. 61-62.) Here, the POSA would have been motivated by the volume/viscosity and interpatient variability problems to follow the prior art's suggestion to nano-size megestrol acetate. (A22; A28-A33.) By contrast, in *Eibel* and *Nomiya*, there was no prior art suggestion to make the changes the inventor made. 261 U.S. at 58-64; 509 F.2d at 573. In *Leo* and *Sponnoble* the prior art actually taught away from what the inventor did. 726 F.3d at 1353-57; 405 F.2d at 587.

The *Wiseman* court specifically distinguished *Eibel* on the ground that there is no patentability if a previously unknown problem is inherently solved when the POSA follows the prior art's teachings to take the same claimed steps while addressing a known problem. 596 F.2d at 1023 ("Although there may be patentable invention where the solution is obvious *after* the discovery of the cause of a problem, [citation to *Eibel*], a different situation exists where the solution is *obvious from the prior art* which contains the same solution for a similar problem,….") (italics added).

Here, the District Court found that the reduced food effect is inherent in following the prior art's suggestions to nano-size megestrol acetate in order to address the known volume/viscosity and interpatient variability problems. (A27.) The Court relied on Dr. Beach's explanation of the straightforward mechanism by which the reduced food effect occurs. (A27.) The reduction in particle size improves bioavailability, so that the assistance of the release of additional bile and enzymes stimulated by digestion of fatty foods is no longer needed. (*Id.*; A3108 at 97:6-19; A3112 at 10:25-12:5.)

Furthermore, nano-sizing is the only means for obtaining the claimed reduced food effect that is disclosed and claimed in the patent-in-suit. (A57 at 8:54-63.) No other mechanism is said to produce the reduced food effect. Thus,

per the patent's own teachings, the reduced food effect is inherent to the nano-sizing of megestrol acetate.

The POSA would have been especially drawn to the "particularly preferred" size of less than 300 nm size disclosed and claimed in EPO '215 for a nano-sized megestrol acetate cancer agent. (A14939 at [0023]; A14947-A14948 at claims 1, 3.) The particle size is in the "sweet spot" that Dr. Beach testified produces the reduced food effect. (A3113 at 15:15; A3119 at 40:5.) Accordingly, by following the teachings of the prior art, the POSA would have inherently obtained the claimed reduced food effect.

"It is well settled that a patent cannot be properly granted for discovery of a result which would flow naturally from the teachings of the prior art." *In re Libby*, 255 F.2d 412, 414 (CCPA 1958). *E.g.*, *Gen. Elec. Co. v. Jewel Incandescent Lamp Co.*¸ 326 U.S. 242, 246-247 (1945) (By following the prior art teachings of Wood plus Kennedy, one "inherent[ly]" obtains what the patentee claimed.); *Wiseman*, 596 F.2d at 1023 ("[T]he Ruppe brake, when provided with Benini's grooves, would inherently overcome the steam or vapor cause of the problem, relied on for patentability by appellants."); *Libby*, 255 F.2d at 415 ("[T]he proposed combination of the Richardson and Lewis disclosures will inherently result in the overcoming of the suds inhibiting effect of the fatty impurities."); *In re Paul*, 252 F.2d 306, 309 (CCPA 1958) ("This desirable result is inherent in the obvious

combination of the references and hence does not confer patentability on the claimed combination.").

Appellants attack the Court's finding of inherency by arguing that one would not always get a reduced food effect because one could fiddle with various parameters. (Appellants' Bf. 38-42.) One, of course, can always make something not work, but that is not what the POSA would have done. She would have turned her attention to achieving a good result. Appellants' arguments are hindsight-driven deviations from the teachings of the prior art presented for the litigation-induced purpose of creating an inferior result, which is an exercise that the POSA would have found perverse.

Furthermore, Appellants' legal reasoning is erroneous. Appellants argue that TWi had to prove that "**all** nanoparticulate formulations of megestrol acetate" inherently have the claimed properties. (Appellants' Bf. 41-42 (Appellants' bolding).) The relevant inquiry, however, is not about "all" formulations, but only about those covered by the claims. Furthermore, "claims are unpatentable when they are so broad as to read on obvious subject matter even though they likewise read on non-obvious subject matter." *In re Mraz*, 455 F.2d 1069, 1072-73 (CCPA 1972); *accord*, *In re Lintner*, 458 F.2d 1013, 1015 (CCPA 1972); *see also Alcon*, 687 F.3d at 1368 (invalid when portion of claimed range is obvious). Accordingly, the inherent presence of reduced food effect in *any* obvious formulation within the

scope of the claims is sufficient to support obviousness. It does *not* have to exist in *all* of them.

Appellants criticize TWi for arguing both nonenablement and obviousness. (Appellants' Bf. 41.) Unlike obviousness, support for enablement must be commensurate with the scope of the claims. *Magsil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012) ("[A] patentee chooses broad claim language at the peril of losing any claim that cannot be enabled across its full scope of coverage."); *Alcon*, 687 F.3d at 1368 ("If everything up to 0.001% w/v is admittedly not enabled, then the entire claim is invalid."). That means that the absence of the claimed reduced food effect in some formulations otherwise within the scope of the claims establishes lack of enablement even though, as just explained, it does not defeat obviousness. Accordingly, there is nothing inconsistent about TWi arguing both obviousness and nonenablement.

Appellants quote the following from a footnote in *Allergan v. Sandoz*:

> The evidence of record does not establish that the dose reduction "from 3 to 2 times a day without efficacy" limitation is an inherent property or a necessary result of the administration of 0.2% brimonidine and 0.5% timolol in a single composition. Of course, it **may** be true that the mere administration of 0.2% brimonidine and 0.5% timolol twice daily in any fixed combination formulation inherently produces the claimed result. Alternatively, it **may** also be true that only certain fixed-combination formulations produce this result.

(Appellants' Bf. 42 quoting 726 F.3d 1294 n.1 (Appellants' bolding).) This footnote does not assist Appellants. In the sentence to which the footnote is appended, the court had just explained that inherency was not at issue because Sandoz had not pressed that argument. 726 F.3d at 1294. Therefore, the footnote's discussion of inherency was *dictum*. The *ratio decidendi* was the holding that Sandoz had failed in its attempt to prove that the prior art taught that a loss of efficacy problem could be addressed by the claimed approach. *Id.* By contrast, here the prior art repeatedly states that food effect problems can be addressed by nano-sizing. (A23; A3116 at 27:9-20; A14905; A14925; A14955; A14956; A14994; A15634.) In the footnote the court did not explain the implications of its comment that only some of the claimed formulations may have had the claimed special property. 726 F.3d at 1294 n.1. As explained above, however, the claims are invalid for obviousness when *any* obvious formulations within the scope of the claims inherently have the special property. The claims are invalid for nonenablement when some of the claimed formulations lack that property.

B. The dependent claims add nothing patentable.

As just explained, the food effect limitations of Claims 1, 4, and 5 do not aid patentability because they recite inherent properties. The other claims do not add anything patentable.

Appellants do not argue the separate patentability of dependent Claims 2, 10, 21, and 24, which recite use of the method in the treatment of HIV or AIDS, or dependent Claims 16-17 and 30-31, which add recitations about the surface stabilizer. As explained in Sections III.F.1 and III.F.5 of the Counter-Statement Of The Case, the prior art teaches these features. Appellants do not contend otherwise.

The remaining claims add certain C_{MAX} measurements, but nothing more about food effects. Dependent Claims 7 and 19 add recitations comparing the mean C_{MAX} of the nanosized formulation with the prior art nonnanosized formulation; they do not add any recitations comparing Fed C_{MAX} with Fasted C_{MAX}. (A75-A76.) Dependent Claims 12-14 and 26-28 add recitations concerning the minimum C_{MAX} obtained, but add nothing comparing Fed C_{MAX} with Fasted C_{MAX}. (A75-A76.)[5] Dependent Claims 15 and 29 add recitations of a range for mean C_{MAX} after a single administration in a fasted state, but do not add anything comparing it to Fed C_{MAX}. (A75-A76.) As explained in Sections III.F.2-4 of the Counter-Statement Of The Case, these C_{MAX} measurements do not distinguish from the prior art.

[5] Appellants now contend that these claims are reciting a minimum C_{MAX} in the fasted state, even though they did not request that construction in the district court. (Appellants' Bf. 10, 40; A20071-A20089.) That construction is not consistent with the specification and other claims in which C_{MAX} refers to the fed state as well as the fasted state. See Section III.C of the Counter-Statement Of The Case.

Furthermore, these additional C_{MAX} recitations merely involve administering the drug to a patient and claiming the resulting serum concentrations — the very thing that *Santarus* holds cannot save an otherwise obvious formulation from invalidity. 694 F.3d at 1354 ("[A]n obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the serum concentrations.").

IV. There was no clear error in the District Court's findings regarding the inadequacy of the evidence of alleged secondary considerations and no legal error in its weighing of the evidence.

Tellingly, Appellants do not argue that others failed in attempts to nano-size megestrol acetate or that such was greeted with skepticism. Appellants have abandoned reliance on commercial success and copying as indicia of nonobviousness. Unexpected results and long felt need are the only objective indicia of nonobviousness that Appellants urge on appeal. (Appellants' Bf. 57-64.) The District Court rejected Appellants' attempts to prove those factors. (A37-A39.) This Court "give[s] deference to a lower court's factual findings regarding evidence of secondary considerations." *Bristol-Meyers*, 752 F.3d at 978.

A. Alleged unexpected results.

Appellants failed in their attempt to prove the predicates for relying on an unexpected result. *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007); *Pfizer v. Apotex*, 480 F.3d at 1371.

First, as explained above in Argument Section II, there was no clear error in the District Court's refusal to find that the so-called "reduced food effect" was in fact unexpected. Not only was nano-sizing's ability to reduce food effects already known, Appellant Alkermes had already used it to justify the patentability of the prior art '684 patent. (A23 citing A14905, A14925 ¶ 9.)

Second, even assuming for the moment that the reduced food effect were an "unexpected" result, the evidence must show that the alleged unexpected result "is commensurate with the scope of the claims." *Allergan v. Apotex*, slip op. 18, 23. All the claims recite a particle size of "less than about 2000 nm" and a dose range of "about 40 mg to about 80 mg." (A74-A77.) TWi's expert Dr. Beach explained that the reduction in food effect does not occur throughout the entire claimed ranges. (A3113 at 15:10-16:3; A3119 at 38:17-40:14; A3120 at 41:6-42:1.)

Even assuming *arguendo* (and contrary to the evidence) that the claimed reduced food effect were both unexpected and commensurate with the scope of the claims, "an unexpected result or property does not by itself support a finding of nonobviousness." *Bristol-Meyers*, 752 F.3d at 976; *see also id.* at 977 n.3 (citing examples of when this Court has "held an invention to be obvious despite findings of unexpected results."). The alleged unexpected result must be weighed along with the other evidence, and when that is done it is overwhelmed by the strong showing here of obviousness based on the prior art. *Pfizer*, 480 F.3d at 1372

("[E]ven if Pfizer showed that amlodipine besylate exhibits unexpectedly superior results, this secondary consideration does not overcome the strong showing of obviousness in this case."); *Richardson-Vicks, Inc. v. Upjohn Co.*, 122 F.3d 1476, 1484 (Fed. Cir. 1997) ("The unexpected results and commercial success, although supported by substantial evidence, do not overcome the clear and convincing evidence that the subject matter sought to be patented is obvious.").

Contrary to Appellants' accusations (Appellants' Bf. 23, 58-60), the District Court did not require Appellants' alleged unexpected result to be linked to the interpatient variability and volume/viscosity motivations to nano-size megestrol acetate. Rather, the District Court's point was that a presumed unexpected reduced food effect would do nothing to undercut those prior art established reasons for making the claimed invention. (A37.) That is consistent with this Court's precedents. *Bristol-Meyers*, 752 F.3d at 976 ("Those additional unexpected properties, however, did not upset an already established motivation to modify a prior art compound based on the expected properties of the resulting compound."); *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1334 (Fed. Cir. 2014) ("The evidence of superior efficacy does nothing to undercut the showing that there was a reasonable expectation of success…."); *Allergan v. Sandoz*, 726 F.3d at 1293 (Motivations other than the unexpected solution of the "afternoon trough" problem were sufficient to establish obviousness.); *In re Mod*, 408 F.2d 1055, 1057

(CCPA 1969) (Obviousness affirmed, despite unexpected result, because the prior art "teachings provide more than adequate reason to those of ordinary skill for making the present compounds.").

B. Alleged solution of long-felt need.

The District Court found that Appellants had not proved that the claimed invention solved a previously long-felt, but unmet, need. (A38-A39.) Appellants rely entirely on the Par-sponsored study reported in the 2007 Wanke paper and Dr. Wanke's testimony about it. (Appellants' Bf. 62-64; A3219 at 54:4-19.) The District Court did not err in giving this evidence little weight as it was generated entirely for marketing purposes. (A3221 at 62:23-63:8.). Appellants never explain how their study conducted five years after patent filing shows a recognition in the art prior to the critical date of a need for the invention that remained unmet.

The District Court found (A38) that this evidence was not commensurate with the scope of most of the asserted claims because the study involved HIV/AIDS patients and only asserted dependent Claims 2, 10, 21, and 24 recite treatment of HIV/AIDS patients. *MeadWestVaco Corp. v. Rexam Beauty & Closures, Inc.*, 731 F.3d 1258, 1264-65 (Fed. Cir. 2013) (Objective evidence of nonobviousness must be commensurate with scope of the claims.); *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008) (same); *In re Harris*, 409 F.3d 1339, 1343-44 (Fed. Cir. 2005) (same). Appellants do not contest that

finding. (Appellants' Bf. 63-64.) Appellants' evidence is also not commensurate with the scope of Claims 2, 10, 21, and 24 because they encompass a broad range of doses and the study tested only one dose of Megace ES. *Harris*, 409 F.3d at 1344. Dr. Beach testified that the claimed effects are not obtained throughout the broad claimed range. (A3120 at 41:6-42:1.)

The District Court also pointed to the equivocal nature of the 2007 Wanke paper's preference for Megace ES, as well as the small differential in weight gain between Megace ES and Megace OS. (A39 ("[T]he researcher's equivocal statement that it 'may be' preferable is simply not enough…."); *id.* n.22 ("The actual difference in mean weight gain between the two formulations was only even, at most, two kilograms.").)

Appellants argue that Dr. Wanke's trial testimony should outweigh the equivocation in her published paper. (Appellants' Bf. 63-64.) At a bench trial, however, it is the judge's job to weigh the evidence and it was not clearly erroneous to credit a pre-litigation article over after-the-fact testimony by a party's expert who could not testify about the clinical benefits of nano-sizing the drug and who was not familiar with the relevant prior art. (A3218 at 52:9-13; A3222 at 67:7-11.) Moreover, the equivocal language in the published paper is all the more striking given that Par—who paid for the research, Dr. Wanke's participaton and the paper's publication—co-authored the paper and allowed "key stakeholders" at

Par to edit it. (A3214 at 35:13-35:25; A3221-A3222 at 62:19-66:14; A6077; A16433; A16436; A16438-A16439; A16455-A16456.) In fact, given Par's participation, it would be a misnomer to call this "objective" evidence of anything.

As to the comparative weight gains, Appellants point to Dr. Wanke's testimony that the small differences found in the study are important. (Appellants' Bf. 64.) Once again, it was the judge's job to weigh the evidence on this factual issue. It was not clearly erroneous for the Court to reject reliance on the 2007 Wanke paper's claim of a "*statistically* significant superior weight gain." (A39 n.22 (court's italics).) For example, Dr. Beach testified that, in fact, the study provided no statistically significant or reliable results. (A3118 at 35:15-36:1.) Indeed, as the Court pointed out, Appellant Par admitted in its guilty plea that it did not have "adequate or sufficient data from well-controlled clinical trials" to support its claims of Megace ES's superior clinical efficacy over Megace OS. (A41 quoting A16240-A16241.) See Section II.B of the Counter-Statement Of The Case. Mr. Boghigian also testified that a variety of factors demonstrated that there was no unmet need solved by the claimed invention. (A3289 at 85:21-87:25.)

The inference sought by a long-felt need argument is that the alleged invention was not so obvious because, if it were, others would have already done it. *In re Fielder*, 471 F.2d 640, 644 (CCPA 1973); Merges, "Commercial Success And Patent Standards: Economic Perspectives On Innovation," 76 Cal. L. Rev.

803, 830 (1988); Whelan, "A Critique Of The Use Of Secondary Considerations In Applying The Section 103 Nonobviousness Test For Patentability," 28 B.C.L. Rev. 357, 367 (1987); Robbins, "Subtests of 'Nonobviousness': A Nontechnical Approach To Patent Validity," 112 U. Pa. L. Rev. 1169, 1172 (1964).

Here, that inference cannot be drawn because Alkermes' prior art Liversidge patents blocked free development by others. (A3146 at 19:9-15; A3052 at 7:13-19.) *Brenner v. Manson*, 383 U.S. 519, 534 (1966) ("To the extent that the patentee has power to enforce his patent, there is little incentive for others to undertake a search for uses" of what is covered by that patent.); *accord, Galderma*, 737 F.3d at 740-41; *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376-77 (Fed. Cir. 2005).

Moreover, because there are "many factors that can lead firms to miss a market opportunity, or to intentionally ignore one, long-felt need should not be relied on to establish patentability" in the absence of "direct proof of failure." Merges, 76 Cal. L. Rev. at 875. Appellants do not argue, and presented no evidence of, actual failures. Thus, this case is very different from *Cyclobenzaprine* where a competitor actually failed in its attempt to do the claimed invention. 676 F.3d at 1081-83.

Appellants' unmet need argument is further undercut by Megace ES's poor performance in the market and the prior art's continuing popularity. *Media Techs.*

Licensing, LLC v. Upper Deck Co., 596 F.3d 1334, 1338 (Fed. Cir. 2010) (assertion of long-felt, unsolved need defeated by continuing success of prior art); Robbins, 112 U. Pa. L. Rev. at 1177 ("The absence of commercial success can have an adverse effect upon the validity of a patent to the extent that it rebuts any inference of a long felt demand."); Whelan, 28 B.C.L. Rev. at 567 ("[T]he patentees must prove that their solutions satisfied the need" such as "by showing that their solutions achieved commercial success.") (footnotes omitted).

Megace ES has never met any of its revenue or prescription targets. (A3284 at 65:21-23.) The Court found that Megace ES's share of the market for megestrol acetate peaked at 23% and has since fallen to 19%. (A41.) That leaves more than three-fourths of that market to the prior art. (A41; A3284 at 67:17-20; A6150-A6151; A15099.) Thus, the market data shows "that physicians haven't embraced this product as offering clinical benefits over what's currently available." (A3289 at 87:23-25.)

C. The District Court correctly weighed the secondary considerations with the other evidence.

Objective indicia of nonobviousness perform the important function of guarding against the dangers of hindsight. *Graham*, 383 U.S. at 36; *Bristol-Meyers*, 752 F.3d at 977. Here, however, the District Court did not fall into using hindsight, nor was hindsight needed, because the prior art provided ample teachings directing the POSA to the claimed invention. The strong evidence of

obviousness far outweighs the alleged evidence of nonobviousness on "the scales of patentability." *Graham*, 383 U.S. at 36; *Lyons*, 364 F.2d at 1016.

CONCLUSION

The District Court's judgment should be affirmed. If it is not affirmed, the case should be remanded to address the undecided nonenablement, unpatentable subject matter, and lack of standing issues.

Respectfully Submitted,

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Par Pharmaceutical, Inc. v. TWi Pharmaceuticals, Inc., 2014-1391

CERTIFICATE OF SERVICE

I, Robyn Cocho, being duly sworn according to law and being over the age of 18, upon my oath depose and say that:

Counsel Press was retained by HUSCH BLACKWELL LLP, Attorneys for Appellee to print this document. I am an employee of Counsel Press.

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July 31, 2014

/s/ Robyn Cocho
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CERTIFICATE OF COMPLIANCE

Undersigned counsel certifies that:

This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B). The brief contains **13,780** words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

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Date: July 31, 2014

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